REMARKS

Claims 15-20 and 37-40 were pending and under consideration. No claims are amended, cancelled, or added in this response, so Claims 15-20 and 37-40 remain pending and under consideration.

Applicants note with appreciation the PTO's withdrawal of the finality of the previous rejection, withdrawal of the obviousness-type double patenting rejection, and acceptance of the substitute drawings.

I. Rejection of Claims 15-20 and 37-40 under 35 U.S.C. § 112, Second Paragraph

Claims 15-20 and 37-40 stand rejected as allegedly indefinite over the recitation of "immunologically reactive." Applicants respectfully submit that one of skill in the art can understand the bounds of a claim that recites the term "immunologically reactive," and thus the rejected claim are not indefinite.

A. The Legal Standard

Under 35 U.S.C. § 112, second paragraph, a claim must particularly point out and distinctly claim the subject matter which Applicants regard as their invention. *See* 35 U.S.C. § 112, second paragraph. This statutory mandate is met when "one skilled in the art would understand the bounds of the claim when read in light of the specification." *See Personalized Media Communications, LLC v. International Trade Commission et al.*, 161 F.3d 696, 48 USPQ2d 1880 (Fed. Cir., 1998). "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *See id.*, quoting *Miles Lab., Inc. v. Shandon, Inc.* 997 F.2d 870, 238 USPQ2d 1123 (Fed. Cir., 1993).

B. Claims 15-20 and 37-40 are not Indefinite

Applicants respectfully submit that one of skill in the art can understand the bounds of the term "immunologically reactive." As stated in the response filed November 9, 2001, and acknowledged by the PTO in the Office Action mailed May 5, 2003, the terms "immunologically" and "reactive" have acquired art-recognized definitions. Applicants respectfully submit that one of ordinary skill in the relevant art would read the art-recognized definition of "immunologically" in combination with the art-recognized definition of "reactive" to determine the bounds of the term "immunologically reactive." Such combination of the definitions of "immunologically and "reactive" is well within the ordinary skill of one in the art.

Further, Applicants respectfully submit that the PTO has repeatedly found that one of skill in the art can understand the bounds of the term "immunologically reactive" as

evidenced by issuance of many claims reciting this term. Indeed, a search of the publicly-available PTO database for the term "immunologically reactive" in the claims of issued patents, conducted on October 6, 2003, reveals 167 issued U.S. Patents that recite the term "immunologically reactive" in the claims. The results of this search are attached hereto as **Exhibit A**. While some of these patents probably define the term "immunologically reactive" in the specification, at least some do not provide such an explicit definition.

For example, Claim 1 of U.S. Patent 5,334,394 ("the '394 patent;" attached hereto as **Exhibit B**) recites the phrase "immunologically reactive." The '394 patent was filed on January 4, 1993, and does not contain in its specification an explicit definition of the term "immunologically reactive." Nonetheless, the PTO presumably deemed the bounds of the claims of the '394 patent to be understandable by the ordinarily-skilled artisan prior to issuance. Accordingly, the PTO found that one of skill in the art can recognize the metes and bounds of the term "immunologically reactive" at least as early as January 4, 1993, long before the earliest priority date of the present application. Other examples of claims that recite the term "immunologically reactive" without an accompanying explicit definition in the specification may be found in, *inter alia*, U.S. Patent Nos. 5,378,814 and 5,520,914, attached hereto as **Exhibit C** and **Exhibit D**, respectively. Thus, the PTO has repeatedly found the term "immunologically reactive" to be sufficiently defined for one of skill in the art to recognize the metes and bounds of this phrase.

Therefore, because one of skill in the art can recognize the bounds of the phrase "immunologically reactive," Claims 15-29 and 37-40 are not indefinite. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 15-20 and 37-40 under 35 U.S.C. § 112, second paragraph.

II. The Rejection of Claims 15-17, 19, 20, 37, and 39 under 35 U.S.C. 102(e)

Claims 15-17, 19, 20, 37, and 39 stand rejected as allegedly anticipated by U.S. Patent No. 5,811,523 to Trinchieri *et al.* ("the '523 patent") in view of U.S. Patent No. 5,780,597, Carter *et al.*, 1997, *Hybridoma* 16(4), and Colman *et al.*, 1994, *Res. Immunol.* 145(1):33-36. In particular, the PTO asserts that the '523 patent teaches a polyclonal and monoclonal antibody to the human cytokine NKSF heterodimer that specifically reacts with the 35 kD subunit of NKSF. In more recent parlance, NKSF has been renamed as IL-12.

Further, the PTO asserts that the antibody taught by the '523 patent inherently has the same functional properties as the antibodies of the present invention. The PTO characterizes such functional properties as "inhibiting IL-12 stimulated PHA activated human lymphoblast proliferation" and "inhibiting IL-12 stimulated IFN-γ proliferation." Accordingly, the PTO

asserts that the burden is on Applicants to show a non-obvious difference between the cited reference and the claimed invention. In response, Applicants respectfully submit that the '523 patent does not teach each and every element of the claimed invention and the antibody taught by the '523 patent does not necessarily possess the same properties as the antibodies of the present invention. Accordingly, Applicants respectfully submit that the rejection of Claims 15-17, 19, 20, 37, and 39 as anticipated by the '523 patent is in error.

A. The Legal Standard

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. *See* M.P.E.P. § 2131. Thus, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly "insubstantial" and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir., 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir., 1985), the Federal Circuit explained that even if the prior art teaches " substantially the same thing" as the claimed invention, the reference still cannot anticipate the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

However, an element of the claimed invention may be described either inherently or explicitly. *See* MPEP § 2112. "In relying on a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *See Ex parte Levy*, 17 U.S.P.Q.2d 1461 (Bd. Pat. App. & Inter., 1990) (emphasis original). Thus, to establish inherency, the PTO must show that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by mere probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *See In re Robertson*, 49 U.S.P.Q.2d 1949 (Fed. Cir., 1999). Thus, to establish that an element is inherently taught by a cited reference, the PTO must show that the element is necessarily present in the teaching of that reference. Only after the PTO makes such a showing does the burden shift to Applicants to show that there is an non-obvious difference between the claimed invention and the cited art. *See* M.P.E.P. § 2112.

B. The Antibody of the '523 Patent does not Necessarily have the Structural and Functional Properties of the Antibodies of the Present Invention

Each of Claims 15 and 16 recites a monoclonal antibody that immunologically reacts with the p75 heterodimer of human IL-12, but not any epitope of the p40 subunit. These monoclonal antibodies neutralize at least about 90% of the bioactivity of human IL-12 in either of two specific assays when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. The neutralization of bioactivity of human IL-12 can be assessed in either an IL-12 stimulated PHA-activated human lymphoblast proliferation assay or an IL-12 stimulated IFN-γ production assay. Thus, the antibodies of the present invention neutralize at least about 90% of the bioactivity of human IL-12 when the antibody and human IL-12 are present at defined concentrations, as recited by, for example, Claims 15 and 16. Claims 17, 19, 20, 37, and 39 ultimately depend from either Claim 15 or 16 and thus all allegedly anticipated claims recite the above-described limitation.

The '523 patent does not explicitly teach that the antibodies described therein can neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Indeed, the '523 patent does not characterize the described antibody in any way beyond the specificity of the antibody for NKSF or one of the subunits thereof. Thus, for the '523 patent to anticipate the claims of the present invention, the PTO must show that the antibody taught by the '523 patent inherently neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. For this limitation to be inherently described in the '523 patent, the antibody that specifically binds IL-12 must also necessarily neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml.

Applicants respectfully submit that the antibodies that specifically bind human IL-12 as taught by the '523 patent do not necessarily neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. In fact, the present application compares the ability to neutralize human IL-12 bioactivity of the antibodies of the invention to that of an antibody identified as 20C2. 20C2 specifically binds the p75 heterodimer of IL-12, but does not react with either the p35 or the p40 subunit alone. *See*, for example, D'Andrea *et al.*, 1992, *J. Exp. Med.* 176:1387-1398 at page 1391, Col. 2, bridging paragraph from page 1390 and at page 1395, Col.2, second full paragraph (Reference C4 of record).

The present application demonstrates that the while 20C2 specifically binds IL-12, it nonetheless does not neutralize at least about 90% of the bioactivity of human IL-12 when those molecules are present at the recited concentrations. *See*, for example, the specification at page 4, line 25 to page 6, line 2 and Figures 3 and 5. Figure 3 shows that the monoclonal antibodies of the invention can neutralize at least about 90% of the bioactivity of 0.25 ng/ml human IL-12 as assessed by an IL-12 stimulated PHA-activated lymphoblast proliferation assay, while 20C2 simply cannot. Likewise, Figure 5 shows that the monoclonal antibodies of the invention can neutralize at least about 90% of the bioactivity of 0.25 ng/ml human IL-12 in an IFN-γ production assay, while 20C2 cannot. Thus, though 20C2 specifically binds human IL-12, it does not neutralize at least about 90% of human Il-12 bioactivity.

As shown by the foregoing, the present application provides an example of an antibody that specifically reacts with human IL-12 but does not neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Thus, it is clear that an antibody that specifically reacts with human IL-12 does not necessarily neutralize at least about 90% of the bioactivity of human IL-12 under the defined condition. Accordingly, the '523 patent does not inherently teach this element of the invention as presently claimed.

Parenthetically, Applicants note that it is irrelevant whether the antibody taught by the '523 patent can inhibit an indeterminate amount of IL-12 stimulated PHA activated lymphoblast proliferation or IL-12 stimulated IFN-γ production. As discussed above, the antibody that specifically binds IL-12 as described by the '523 patent must necessarily neutralize 90% of the bioactivity of IL-12 under the appropriate conditions as measured by one of these assays to inherently teach the presently claimed antibodies.

Moreover, because an element of the invention as claimed is not inherently described by the '523 patent, the PTO cannot shift the burden to Applicants to show that the claimed invention is non-obvious over the '523 patent. As discussed above, only when the PTO sets out a basis in fact and/or technical reasoning to show that the cited reference necessarily possesses the allegedly inherent characteristic can the burden be shifted to Applicants to show a non-obvious difference between the reference and the claimed invention. The PTO has not shown and cannot demonstrate that the antibodies of the '523 patent necessarily neutralize at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Accordingly, the burden remains on the PTO to prove that the presently claimed antibodies are not patentable in order to reject the claims of the present application.

As shown by the foregoing, the '523 patent does not teach, either explicitly or inherently, each and every element of the invention as presently claimed. Further, the PTO cannot shift the burden to Applicants to show that the claimed invention is non-obvious over the '523 patent because an element of the invention as presently claimed is not inherently described by the '523 patent. Therefore, Applicants respectfully submit that the rejection of Claims 15-17, 19, 20, 37, and 39 under 35 U.S.C. § 102(b) as anticipated by the '523 patent is erroneous and earnestly request its withdrawal.

III. The Rejection of Claims 15, 16, 18, and 38-40 under 35 U.S.C. § 103(a)

Claims 15, 16, 18, and 38-40 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '523 patent in view of U.S. Patent No. 5,780,597; Carter *et al.*, 1997, *Hybridoma* 16(4); Colman *et al.*, 1994, *Res. Immunol.* 145(1):33-36; and Bendig, 1995, *Methods: A Companion to Methods in Enzymology* 8:83-95. Applicants submit that the combination of the cited references do not teach each and every element of the invention as presently claimed, and thus the rejection of Claims 15, 16, 18, and 38-40 as obvious is in error.

A. The Legal Standard

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention prima facie obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. The Cited References do not Teach or Suggest Each and Every Element of the Claimed Invention

The PTO supports the rejection of Claims 15, 16, 18, and 38-40, in part, on the same portions of the '523 patent as were cited in the rejection of Claims 15-17, 19-20, 37, and 39 as anticipated. In particular, the PTO relies upon the '523 patent to teach or suggest an antibody that neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml.

As shown in Section II, above, the '523 patent in no way teaches or suggests an antibody that neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml, as recited by, for example, Claims 15 and 16. This deficiency of the '523 patent is not remedied by the disclosures of the other cited references; none of the cited references teach or suggest an antibody that neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. Accordingly, the combination of cited references do not teach or suggest each and every element of the invention as presently claimed.

Because each of Claims 18 and 38-40 depends from either Claim 15 or 16, each incorporates the limitation that the claimed antibody neutralizes at least about 90% of the bioactivity of human IL-12 when the concentration of the antibody is 0.5 μg/ml and the concentration of human IL-12 is 0.25 ng/ml. As shown above, none of the cited references teach or suggest this element of the invention as presently claimed. Accordingly, Applicants respectfully submit that the rejection of Claims 15, 16, 18, and 38-40 as obvious under 35 U.S.C. § 103(a) is erroneous and earnestly request its withdrawal.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims fully comply with all statutory requirements for patentability. Accordingly, Applicants respectfully request that the PTO reconsider the claims of this application with a view towards allowance. The Examiner is invited to telephone the undersigned attorney, if the Examiner feels that a teleconference could help resolve any outstanding issues.

Respectfully submitted,

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